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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CLOW, LORI A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,967	RICH ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5 August 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicants' arguments, filed 5 August 2005, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 2 and 3 are currently pending.

Information Disclosure Statement

The Information Disclosure Statement filed 5 August 2005 has been considered. A signed copy of PTO Form 1449 is included with this Office Action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 55-81 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. It is not clear what result is produced by the said method. The "usefulness" of "a method comprising obtaining a sample, generating a gene expression profile, determining the

nucleotide sequence of the mRNA in the profile, predicting the amino acid sequence, predicting the mass of the polypeptide encoded by the mRNA, generating a protein profile, and determining the presence or absence of the polypeptide in the protein profile" is not apparent, as there is now no step of correlating gene and protein expression, nor is there a step of correlating the candidate polypeptide with a polypeptide encoded by an mRNA. Furthermore, the mRNA is an unidentified mRNA, such that the utility of identifying it without knowing what exactly it encompasses is not immediately useful. It is noted that in order for the claimed method to be useful for these purposes, other information is required, such as a correlation between gene and protein expression from two samples, for example. Utilities that carry out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (See MPEP 2107.01). Further, as set forth in Brenner v. Mason (148 USPQ 689 (1966)) and In re Ziegler (26 USPQ2d 1600), the "usefulness" of an invention must be immediately apparent to those familiar with the technological field of the invention. As further research and method steps would be required to "use" the instant method the apparent result of the method is not "immediately useful" and lacks utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to obtain a biological sample; generating **a gene expression profile, thereby identifying an mRNA** expressed in the sample; determine the nucleotide sequence of the mRNA; predict the amino acid sequence of the polypeptide encoded by the mRNA; predict the mass of the encoded polypeptide; generate a protein profile of the polypeptides in the sample by mass spectrometry; and determine the presence or absence in the protein profile of a polypeptide having a mass that correlates to the predicted mass of the encoded polypeptide. For the reasons discussed below, this constitutes undue experimentation.

b) and c) The specification outlines the following with respect to the gene expression profile and the mRNA of interest:

"Comparing the gene expression profiles of different cells is a process called differential gene expression. This method can provide information about the genes that are responsible for the different phenotypes of cells. Genes that are differentially expressed in healthy and

pathologic cells can function as diagnostic markers and are candidate targets for therapeutic intervention. Thus, obtaining accurate profiles of gene expression in different cell types is an important goal (page 1, line 30 to page 2, line 2)".

"Gene expression profiling is used to select a candidate transcript or transcripts that are expressed in a cell. The transcripts are typically sequenced and used to deduce the amino acid sequence of the encoded protein. The amino acid sequence is then used to predict and identify physio-chemical characteristics of the protein encoded by transcript, e.g., molecular weight,. isoelectric point, hydrophobicity, hydrophilicity, glycosylation, phosphotylation, epitope sequence, ligand binding sequence, charge at specified pH, or metal chelate binding. The physio-chemical characteristics are then employed to improve the sensitivity and resolution of protein profiling, thereby providing improved information about the proteins encoded by mRNA expressed in a particular cell type. This invention provides methods for making such a correlation and provides other advantages, as well (page 3, lines 10-20)".

"The present invention provides methods that combine RNA and protein expression profiling, to identify genes and the proteins expressed in cells under different conditions, e.g., at different times in the cell cycle, under varying environmental conditions (such as ion influx or efflux; exposure to a toxin; drug; ligand; e.g., a hormone, a cytokine, or a chemokine; or a pathogen such as a virus, bacteria, protozoa, or fungus), under varying pathological conditions, such as cancer, at different times during maturation and differentiation, at different times during development of the organism, during responses such as inflammation, in different tissue types or organs, in different pathological conditions such as cancer or autoimmune disease, between individuals with different phenotypic traits, e.g., responders vs. non-responders to a particular

pharmaceutical drug, etc. The methods of the present invention, e.g., allow one of skill in the art to identify a list of candidate genes expressed in a cell or biological sample, and then to further identify a subset of proteins of interest encoded by the genes of interest (page 4, lines 21-32)".

"Differential profiling (comparison with another cell, e.g., that has a different phenotype, or is at a different temporal or developmental stage, or has been exposed to different environmental conditions, e.g., physical or chemical conditions, etc.) provides useful information about the cell of interest, e.g., genes that are preferentially or selectively expressed in a given cell type. Often, a gene of interest is highly expressed in one cell but not another. In other embodiments, the gene of interest has a similar expression pattern in different cells. In other embodiments, the gene of interest has low expression in one cell as compared to another (page 18, lines 7-14)".

In each preferred embodiment taught, the gene expression profile is generated from biological samples that may somehow be different, such that an mRNA of interest could be identified. However, in the instant claims, only one expression profile is generated from one biological sample. How does one ascertain which mRNA to identify if only one particular cell type is represented, for example? What meaning would one random mRNA have from another in this circumstance (see Utility rejection above)? How would one of skill in the art know which mRNA to identify from the gene expression profile? How is one identifying the mRNA? By sequence size, expression level, some other criteria? Does Applicant simply mean "select" an mRNA, at random? Without such differentiation, such that it is apparent which mRNA to select /identify, the claims are not enabled.

d) The invention is drawn to methods for generating a gene expression profile and identifying an mRNA. However, how does one identify **an** mRNA out of the myriad that are contained in a biological sample such that the instant method is enabled?

e) and g) The prior art indicates that gene expression profiling is used to characterize differences in cell types, such as cancer versus non-cancer to identify potential genes for further study (Alizadeh et al. (2000) Vol. 403, pages 503-511). Alizadeh et al. teach using DNA microarrays to characterize gene expression in B-cell malignancies (abstract). Samples consisted of various cell types, including germinal center B cells, follicular lymphoma, and chronic lymphocyte leukemia (page 504, column 1). Gene expression patterns could be ascertained using this method by comparing the different microarrays. In this fashion, genes that vary in expression with cellular proliferation rates could be identified (page 504, columns 1 and 2).

f) The skill of those in the art of molecular biology and protein chemistry is high.

h) The claims are broad because they are drawn to a method comprising generating a gene expression profile from only one sample. The skilled practitioner would first turn to the instant specification for guidance to practice such methods. However, the instant specification does not provide specific guidance to practice these embodiments, rather the specification indicates that a comparison of differential expression is used to choose or identify the appropriate mRNA for identification. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows gene expression profiling for different cell types. Finally, said practitioner would turn to trial and error experimentation to determine whether a random mRNA could be chosen from a single sample that correlated to protein expression. Such represents undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 recites "identifying mRNA". It is unclear what about the mRNA is identified. Is it the highest expressed mRNA, the lowest, the one that exhibits change in expression? (see enablement rejection above). Clarification is requested.

Claim 67 recites "wherein mRNA is differentially expressed in two biological samples". This is unclear, as the prior steps include only one biological sample. Clarification is requested.

Claim 73 recites "in step (d), predicting a post-translational modification of the encoded polypeptide" etc... It is unclear if these steps (d)-(g) are steps in addition to steps (d)-(g) in claim 55 or if they are intended to replace the steps in claim 55. Clarification is requested.

Claim 75 recites steps (i)-(iii). It is unclear in step (i), for example, where the step occurs. Further, in step (ii), there is not even a protein to fractionate before step (f). Finally, what fraction is being retained? The fraction containing the physio-chemical property or some other fraction?

No claims are allowed.

Conclusion

Applicant's arguments with regard to the 35 USC 112, 1st paragraph rejection for lack of enablement are moot in view of the new grounds of rejection set forth above. It is noted that the new grounds of rejection are fully necessitated by amendment.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

September 15, 2005
Lori A. Clow, Ph.D.
Art Unit 1631
Lori A. Clow

MARJORIE A. MORAN
PRIMARY EXAMINER
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9/15/05